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This evaluation has shown that these studies do not offer quantitative data for estimating levels associated with a defined risk.

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Comparing Epidemiologic Studies of Ingested Asbestos for Use in Risk Assessment

by Linda S. Erdreich*

Epidemiologic data can be used in risk assessment in various ways: to calculate the dose-response relationship between exposure levels and adverse effects; to establish ranges of exposure known to be safe or unsafe; to verify an endpoint in humans derived from a route or species extrapolation; to support assumptions necessary for performing extrapolation procedures. These points are illustrated in the risk assessment for exposure to asbestos in drinking water.

A previous risk assessment for asbestos, the EPA's Ambient Water Quality Criteria (AWQC) for Asbestos, was derived from cohort studies of inhalation exposure. Epidemiologic studies of ingested asbestos, all of geographical correlation design, were compared on the basis of their ability to add information in support of both the route extrapolation and low-dose extrapolation used in this risk assessment. Results of these ingestion studies were inconsistent due to variable ability to detect a risk from chronic low-level exposure. After preliminary comparisons of factors that determine scientific validity and statistical power, two ingestion studies were selected to determine if they had the potential to detect the risk predicted by the AWQC.

This evaluation has shown that these studies do not offer quantitative data for estimating levels associated with a defined risk. Due to short exposure duration and limited power, clearly safe and clearly unsafe ranges could not be definitely identified. The most appropriate ingestion studies suggest, but do not prove, the endpoint derived from the route extrapolation in the AWQC.

Introduction

The incorporation of information from epidemiologic studies into health risk assessment depends on the nature of the available scientific data and the nature of the unresolved issues. Epidemiologic data can be used in health risk assessment for a variety of purposes. The process of screening and comparing epidemiologic studies for use in health risk assessment will be described for ingested asbestos.

The EPA's Ambient Water Criterion (AWQC) for Asbestos for human health is based on human inhalation studies; therefore, data on the health effects of human exposure via ingestion are necessary to verify this route extrapolation. Ingested asbestos studies are evaluated to select those appropriate for use in risk assessment. Central to this evaluation is the comparison of the increased risk predicted on the basis of the AWQC with the estimated ability of a given study to detect this risk.

An integral aspect of screening studies for use in risk estimation is the critical analysis of all the strengths and weaknesses of relevant aspects of each study. Because Marsh, in his presentation at this workshop (*1*), did this in great detail for the epidemiologic studies of ingested asbestos, this analysis will not be repeated here.

Background

One of EPA's many endeavors in the area of health risk assessment has been the Ambient Water Quality Criteria Documents (AWQCD) (*2*). The Clean Water Act of 1977 (P.L. 95-217) required these documents to calculate criteria for 65 toxic pollutants or pollutant categories and to summarize and reflect accurately current knowledge of the kind and extent of all effects on human health that would be expected from the presence of pollutants in ambient water. The water quality criteria for human health are a scientific assess-

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ment of ambient levels of a pollutant that is estimated to result in defined levels of risk for a given carcinogen or no-observed-adverse-effect levels for toxicants. States may use these criteria and, after considering local environmental conditions and human exposure patterns, incorporate them into regulations as standards.

Obviously, the ideal source of data for assessing human risk is exposure situations in humans via the appropriate exposure route. In the absence of quantitative route-specific data for humans, it is sometimes necessary to substitute either human data from another route of exposure or dose-response data in animals. Extrapolations from route to route (e.g., inhalation to ingestion), from animals to humans, or from high to low doses are performed according to procedures documented in the *Federal Register* (*3*). These procedures are constantly being refined and apply to situations in addition to those of ambient water quality—hazardous waste sites, for example.

Basis of the Current AWQC for Asbestos

The AWQC for asbestos is derived from exposure-response data in three epidemiologic studies involving large occupational cohorts exposed for a working lifetime to airborne asbestos. These workers, who were followed over time to ascertain causes of death, were found to have an increased incidence of peritoneal mesothelioma and gastrointestinal (GI) cancers. In two of the studies used to calculate the criterion, GI cancers included esophagus, stomach, small intestine, colon and rectum. In the third study, liver, gallbladder and pancreas were also included. The assumption that these cancers can also be caused by ingested asbestos was supported by positive associations for digestive tract sites in the geographic correlation study of ingested asbestos in the California study first reported by Kanarek et al. (*4*). The route extrapolation is also supported by the fact that most of the inhaled asbestos is cleared from the respiratory tract and ingested by normal body processes.

The average of the excess deaths in all three cohorts exposed via inhalation was related to the average exposure index. This average was also extrapolated to low dose levels to estimate criteria levels; e.g., the ambient water level necessary to keep lifetime excess cancer risk to an exposed population below 10^{-5} is 0.3 million fibers of all sizes/L (0.3 MFL), assuming ingestion of 2 L water/day and 70 yr exposure (*2*). According to EPA guidelines (*3*), the extrapolation to low dose is linear when using human data and does not include calculation of an upper 95% confidence limit as when the extrapolation is calculated from animal data. Because both a route extrapolation and a low-dose extrapolation were used, the criteria would be strengthened by support from human studies of exposure by ingestion at ambient levels.

Uses of Epidemiologic Data in Risk Assessment

Epidemiologic data can be used in risk assessment for a variety of purposes: (1) to estimate the dose-response relationship in order to identify the highest concentration level at which no adverse health effects or a defined low-level of adverse health effects are anticipated; (2) to establish ranges of exposures that are or are not associated with an adverse effect; (3) to support or verify an endpoint identified from a different route of exposure or from experiments in animals; (4) to support general assumptions necessary for performing extrapolation procedures.

These purposes depend on characteristics of the data as determined by study design, power, and quality of the exposure data. For example, quantitative exposure-response data are necessary for quantitative estimates described in points (1) and (2). Studies with qualitative exposure data are useful for point (3) to verify a route extrapolation or a target organ for a suspected carcinogen. To support extrapolation processes, point (4) usually requires a body of evidence, such as the human epidemiologic studies of carcinogens that correlate with animal studies.

The derivation of the existing asbestos AWQC for human health from epidemiologic data illustrates point (*1*). That assessment required an extrapolation from the inhalation exposure route to the ingestion route because existing epidemiologic studies of ingested asbestos were of geographic correlation (ecological) design not applicable for quantitative risk assessment.

Research on the health effects of asbestos has continued since the publication of the AWQC and has contributed information that can be used to reevaluate this risk assessment. More recent studies designed to evaluate the association between ingested asbestos and cancer can be used to address point (*2*), distinguishing safe from unsafe ranges of exposure, and point (*3*), verifying the association between ingested asbestos and certain cancers. Point (*4*) describes the use of a broad epidemiologic data base and is presented for com-

pleteness, although data on asbestos cannot yet be used for this purpose.

Comparing Epidemiological Studies of Ingested Asbestos

All nine ingestion studies compared in this discussion are ecological studies in which readily accessible vital statistics, such as mortality or incidence, are correlated with the exposures assumed to be experienced by these populations. Geographic correlation studies usually serve as screening devices to indicate associations that could be examined subsequently with more precise and powerful analytic designs, such as case control or cohort. The correlation studies were performed to offer a rapid and cost-efficient mechanism for addressing the public health questions of whether areas with asbestos-cement pipe have higher cancer rates. The nine studies cited (*4–12*), which were performed in five geographic areas, lack precision due to the possible misclassifications inherent to this study design in which residence in an area is assumed to reflect lifetime exposure to that water supply. Inferences that can be made are weak and insufficient for establishing a causal relationship. These studies do, however, make it feasible to incorporate a sample size sufficiently large to detect small increases in low-probability outcomes such as cancer.

The limitations of these asbestos studies are due in part to characteristics inherent to the problem of studying the effects of low-level exposures on rare outcomes such as cancer. Even at the high occupational exposure levels, relative risks for mortality following inhalation exposures ranged from 1.5 to 2.5 for GI sites (*13*). The limitations listed in Table 1 suggest that, to establish the dose-response gradient by epidemiologic studies, an analytic (case-control or cohort) study of sufficient sample size would be required to detect the low relative risk expected.

This table also lists approaches to handle these limitations. Many have been attempted in the studies to date. For example, a surveillance system has been initiated in Duluth to follow trends over time (*5*), and studies were initiated in the Puget Sound area, which has high ambient levels (*11*). Confounding risk factors for cancer, such as diet, smoking habits and occupational exposures, are not well evaluated in geographic correlation studies.

The evidence for a causal relationship between a risk factor and disease is often evaluated by comparing the pattern of results among studies. Consistent and repeatable results to support the association are particularly important when the association is weak due to low exposure levels or the low potency of the carcinogen. Table 2 shows that few associations between asbestos and cancer are positive in both sexes, and few are repeated across studies for the same cancer site (*11*). Two sites that show repeated positive associations among studies are the pancreas and stomach, but the latter is not consistently positive for both sexes. Since the AWQC was based on total peritoneal mesotheliomas and "gastrointestinal cancers," mainly of esophagus, stomach, colon and rectum, those sites must be examined together in order to evaluate the AWQC. (Peritoneal mesothelioma is rare and was often omitted from the studies because few cases were reported.)

Table 3 presents results for these sites, as reported only in papers representing two of the areas, Duluth and California (*4–6,9*). Mortality data for Duluth reported for four 5-yr periods did not support an increase, although the data were tested for trend (*5*). Levy et al. (*6*) found that standardized incidence ratios were higher for the two comparison cities than for Duluth. Both reports of cancer incidence in the San Francisco area show an increase in rates with asbestos fiber counts (*4,9*). Conforti et al., who tested the standardized incidence ratios for slope and found the increase for "all digestive tract cancers" significant for white males and for white females, inter-

Table 1. Inherent limitations of studies involving ingested asbestos and possible solutions.

Inherent limitations	Approaches
Exposure duration is short compared to cancer's long latency period (*5–8*)	Increase observation period Maintain surveillance over time
Exposure levels are often low, particularly for asbestos-cement pipe (*7, 8, 12*)	Select study population from high exposure area Increase sample size
Exposure to individuals is not usually assessed in geographical correlation studies (*4–12*)	Design study to examine individual exposures
Probability of outcome is low, requiring extremely large samples	Design study to focus on high-risk groups Use case/control study design to reduce required sample size
Confounding factors exist and can bias results	Control by: stratification or mathematical modeling or restriction of study design to certain areas or individuals

Table 2. Summary of studies of cancer risk in relation to asbestos in water supply by site of neoplasm.[a]

Area	Reference	Site of neoplasm[b]							
		Esophagus	Small intestine	Colon	Rectum	Stomach	Pancreas	Lungs	Peritoneum
Duluth, MN	Mason et al. (*5*)	OO	—	OO	MF	MF	OF	—	—
	Levy et al. (*6*)	OO	OO	OO	OO	MO	MF	—	OO
Quebec	Wigle (*10*)	—	—	OO	OO	MO	OF	MO	—
Connecticut	Harrington et al. (*7*)	—	—	OO	OO	OO	—	—	—
	Meigs et al. (*8*)	—	—	OO	OO	OO	B	OO	—
California	Conforti et al. (*9*) Kanerek et al. (*4*)[c]	MF	OO	OO	OO	MF	MF	OO	OF
Washington	Polissar et al. (*11*)	OO	MF	OO	OO	OO	OO	OO	—
Florida	Millette et al. (*12*)	—	—	—	—	—	OO	OO	—

[a]Adapted from Polissar et al. (*11*).
[b]M, association in males; F, association in females; B, association in both sexes combined; O, no association; —, not studied.
[c]Conforti et al. (*9*) update these results.

Table 3. Summary of studies that assessed the association between all digestive cancers and exposure to asbestos.

Area	Reference	All digestive (ICD 150–158)[a,b]	Digestive tract (ICD 150–154)	Digestive-related organs (ICD 155–158)
Duluth, MN	Mason et al. (*5*)	—	OO	—
Duluth, MN	Levy et al. (*6*)	OO	—	—
California	Conforti et al. (*9*)	MF	MF	MO
Florida	Millette et al. (*12*)	OO	—	—

[a]Code as in eighth revision. International Classification Disease, 1968 (*16*). 150–154: esophagus, stomach, small intestine, colon, rectum. 155–158: liver, gallbladder, pancreas, retroperitoneum.
[b]M, association in males; F, association in females; O, no association; —, not studied.

preted the findings as indicating a positive gradient with asbestos levels (*9*). These increases were consistent when stratified on education and income to control for the potential confounding effect of socioeconomic status.

The inconsistent results across these ingestion studies can be interpreted by examining some factors that affect the ability of a study to detect an association. Factors common to nearly all of these studies include lack of control for confounding risk factors, possible misclassification of exposure due to migration, and lack of assessment of variability in daily water source. These factors are inherent to geographic correlation studies using residence as a surrogate for exposure. Factors that vary among the studies and affect the power of the study to detect an increase include the sample size, frequency of outcome, exposure level, duration of the observation period, and duration of the exposure.

Table 4 shows some of these factors for each of the six areas covered by these nine studies. The Canadian study was seriously biased by the confounding effect of occupational exposures (*10*). In Minnesota, Florida, and Connecticut, duration is barely equal to the suspected 20- to 40-yr latency period for these cancers (*13*). Exposure levels are low in Connecticut and Florida, thus weakening the association. A lack of association in these geographic areas could be attributed to the inability of those studies to detect low risks. The high exposure levels and longer duration in Puget Sound and California suggest that the size of the association would be greater in these areas and therefore more easily detectable.

The ability of a study to detect the risk estimated by the AWQC can be assessed by comparing the estimated excess risk with some measure of the ability of the study to detect this risk. The increased risk expected due to asbestos exposure can be estimated by the number of excess cancer cases predicted by the risk assessment in the AWQC. Several assumptions are required to relate the AWQC-estimated 1×10^{-5} lifetime excess risk for 0.3 MFL to the yearly incidence rate. On assuming that all ages are equally at risk and that the dose-response relationship is linear, an approximation of the excess cancer risk per year can be calculated for the California area as follows:

$$\frac{1 \text{ cancer}}{10^5 \text{ persons} \times 70\text{-yr exposure}} \times \frac{20 \text{ MFL}}{0.3 \text{ MFL}} = 1 \times 10^{-5}$$

where 20 MFL is the middle value of the high

Table 4. Characteristics of the epidemiologic studies that affect the power to detect an association.

Study area (reference)	Duration of exposure, yr	Population exposed	Probable exposure level	Estimate of maximum excess cancer per year[a,b]
Duluth, MN (*6*)	≈16–17	100,000	1–30 MFL	—
Connecticut (*7, 8*)	≈19	576,000	<0.1–0.7 MFL	—
Bay Area, CA (*4, 9*)	>40	1,000,000	4–36 MFL	1×10^{-5}
Puget Sound, WA (*11*)	>50	78,000	200 MFL	10×10^{-5}
Florida (*12*)	>25	46,000	<1–10 MFL (AC pipe)	—
	>25	87,000		
Quebec (*10*)	>50	140,000	80–220 MFL	—[c]

[a]Based on AWQCD estimate of 1×10^{-5} lifetime excess risk of gastrointestinal cancer and peritoneal mesothelioma for 0.3 MFL (1 MFL = 3.33×10^{-5} excess cancers) and on assumptions described in the text.

[b]Calculated only for areas with potential for lifetime exposure at time of study: [1 cancer/(100,000 persons/70 yr)] (20 MFL/0.3 MFL) ≈ 1×10^{-5}.

[c]Results biased by occupational exposures in the exposed group.

exposure group. A similar extrapolation for the Puget Sound, using 200 MFL, estimates an excess rate of GI cancers of 10×10^{-5}. Assuming a background incidence rate of 90/100,000 (0.0009) for California and 75/100,000 for Puget Sound for these cancers, the estimated relative risk for exposed groups is 1.01 for California and 1.1 for Puget Sound. There are two other areas of uncertainty in these estimates. First, the average age for the 1973 San Francisco–Oakland population up to age 70 is 31 yr, representing average exposure duration, whereas the AWQC is based on 70 yr exposure. This may understate the risk. Alternatively, using incidence instead of mortality may overstate the risk because the incidence rate for GI cancers is approximately twice the mortality rate.

The ability of a study to detect a given risk is its power. It is not appropriate to estimate power for ecological study designs on the basis of sample size alone because of the unquantifiable biases introduced by misclassification. It is possible, however, to determine whether these studies would be at least large enough to detect a difference in the absence of systematic biases by comparing them to cohort studies of similar size for which power can be estimated. A comparison will be made with studies of cohort design because analyses in these studies focus on exposed and unexposed groups (*14*). However, this exercise can tell us only whether a study is too small; it cannot help to determine if the sample size is adequate.

Sample size tables (*14*) show that for an outcome of 0.001, slightly higher than the incidence of all GI cancers, a cohort sample the size of the California study would have an 80% probability of detecting a relative risk of 1.1 at $\alpha = 0.05$. A cohort sample of the size of the Puget Sound study would have an 80% probability of detecting a relative risk of 1.5 at $\alpha = 0.05$. The Puget Sound study reported the results for single sites: a cohort study this size could detect a relative risk of 4 for pancreatic or stomach cancer. If the risk for these exposures is similar to that predicted by the AWQC, and if the assumptions apply, then these correlation studies would probably be too small to detect the expected risk.

While the study in Puget Sound (*11*) was interpreted to be negative, the 6-yr study in California (*9*) suggests a positive association of cancer of the digestive system with ingestion of asbestos. This study need not be ignored simply because less powerful studies do not verify this endpoint. While the multiple statistical comparisons and the ecological design introduce biases that reduce the power, the high significance level of the test for trend suggests some association with asbestos. The increase in "all digestive cancers" was significant with a low relative risk (<1.1) and was associated with the high exposure census tracts (4–36 MFL). This study suggests that any association between GI cancers and asbestos exposure may be limited to specific sites such as the stomach and pancreas. These are relatively rare cancer sites in humans and require large sample sizes to detect an increase. Polissar et al. (*11*) compared all of the studies and concluded that results for pancreatic cancer were the least likely to be due to chance (see Table 2). The case-control study by Polissar et al. in the Puget Sound area presented at this workshop (*15*) offers an opportunity for similar analyses for specific sites. The minimum risk that could be detected was under 2.0 for each sex for the following grouped or single sites: digestive system, colon, respiratory tract, and lungs.

Discussion

The observation that geographic correlation studies of populations exposed to ingested asbestos detected little evidence for an increased cancer risk must be reevaluated in view of the considerations affecting the power of any study. Several of the studies were insensitive due to low exposure levels and short exposure duration. The potential for misclassification in the ecological study design makes it inappropriate to assess power directly, yet negative studies should be interpreted in terms of the risk each has the ability to detect. The maximum sensitivity that could be expected from the potentially valid studies, those performed in California (*4,9*) and Puget Sound (*11*), leads to the conclusion that the ability to detect increased relative risks <2 (100% increase) is questionable. It is possible to summarize these two studies as follows: Little if any risk was detected in studies that were capable only of detecting the increase in GI cancers if it was greater than that predicted by the AWQC.

Summary

This body of evidence, summarized in view of the general uses of epidemiolgoic data in health risk assessment described above, does not offer quantitative data for estimating levels associated with a defined risk. Due to limited statistical power and inherent biases in the study design, clearly safe and clearly unsafe ranges cannot be definitely identified. The results of the study in the Bay Area by Conforti et al. (*9*) suggests, but does not prove, the endpoint derived from the route extrapolation required for the AWQC. These ingestion studies do suggest that the risk is not greater than that estimated from the inhalation studies and may be less. Due to the large number of individuals with potential lifetime exposure to asbestos, even small increases in relative risks are important; therefore, measures to reduce exposure are still indicated.

To resolve the issue of the human health risk of waterborne asbestos, it would be necessary to initiate analytic epidemiologic studies that have greater sensitivity. Examination of available pharmacokinetic and experimental animal data would be useful. If data from animal studies clearly did not support the association between cancer and ingested asbestos, the need for human studies might be circumvented.

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The research described in this paper has been peer and administratively reviewed by the U.S. Environmental Protection Agency and approved for presentation and publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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